CHRONIC TOXICITY SUMMARY

METHYL CHLOROFORM

(1,1,1-trichloroethane, methyltrichloromethane)

CAS Registry Number: 71-55-6

I. Chronic Toxicity Summary

Inhalation reference exposure level	**1,000 µg/m^3 (200 ppb)**
Critical effect(s)	Astrogliosis in the sensorimotor cortex (brain) of gerbils
Hazard index target(s)	Nervous system

II. Chemical Property Summary (HSDB, 1999)

Description	Colorless liquid
Molecular formula	$C_2H_3Cl_3$
Molecular weight	133.42 g/mol
Density	1.3376 g/cm^3 @ 20° C
Boiling point	74.1° C
Melting point	-30.4° C
Vapor pressure	127 torr @ 25° C
Solubility	Soluble in acetone, benzene, methanol, carbon tetrachloride
Conversion factor	5.47 µg/m^3 per ppb at 25ºC

III. Major Uses and Sources

Methyl chloroform is used as a solvent for adhesives and for metal degreasing (ACGIH, 1992). It is also used in the manufacture of vinylidene chloride and in textile processing and dry cleaning. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California, based on the most recent inventory, were estimated to be 25,316,458 pounds of methyl chloroform (CARB, 1999a). Statewide monitored median and mean concentrations of methyl chloroform have been generally declining; decreasing from 0.8 or 1.71 ppb in 1990 to 0.12 or 0.30 ppb in 1996 (CARB, 1999b).

IV. Effects of Human Exposure

A 44-year old woman was diagnosed with peripheral neuropathy following 18 months of occupational exposure to methyl chloroform in a solvent bath (House *et al.*, 1994). There was no

identified exposure to agents known to cause peripheral neuropathy, such as n-hexane or trichloroethylene. The worker reported that she wore protective gloves and a respirator, both of which frequently leaked. Seven months following removal from exposure, the worker showed improved nerve conduction.

Other case reports have identified the nervous system as a target of methyl chloroform toxicity in similar exposure scenarios. Three workers developed distal sensory neuropathy after working with methyl chloroform in a degreasing operation with repeated dermal exposure (Liss, 1988; Howse *et al.*, 1989). Changes were observed in nerve conduction in the upper extremities accompanied by both axonopathy and myelonopathy.

Twenty-eight workers with chronic exposure to high (but unquantified) concentrations of 1,1,1-trichloroethane had significant deficits in memory, intermediate memory, rhythm, and speed based on the Luria-Nebraska Neuropsychological Battery (Kelafant *et al.*, 1994). Deficits in vestibular, somatosensory, and ocular components of balance were noted.

A 13-year-old male died after intentional inhalation of 1,1,1-trichloroethane (Winek *et al.*, 1997). Autopsy findings included tissue congestion of lung, liver and kidney.

Cardiac arrhythmia resulting from heightened cardiac sensitivity to epinephrine has been reported in several case reports of high acute inhalation exposures to methyl chloroform (ATSDR, 1990). There are case reports of arrhythmias persisting for two weeks or more after cessation of exposure to methyl chloroform (McLeod *et al.*, 1987).

An epidemiological study of workers chronically exposed to low levels of methyl chloroform (<250 ppm) found no changes in blood pressure, heart rate, or electrocardiogram (Kramer *et al.*, 1978). This study consisted of 151 workers who had been exposed for more than one year. No neurophysiological testing was done.

Another study of 22 female workers exposed to methyl chloroform (plus 7 unexposed control workers) at concentrations ranging from 110-345 ppm in air for a mean of 6.7 years failed to identify neurotoxicity resulting from methyl chloroform exposure (Maroni *et al.*, 1977). The examination included evaluation for neurologic symptoms, changes in nerve conduction, and psychomotor tests.

Liver disease was observed in a worker exposed to methyl chloroform in a clothing factory screen printing room (Cohen and Frank, 1994). The worker was exposed for a total of 4 years before occupational exposure was identified as the cause of the liver disease. The worker sprayed an adhesive (containing 65% methyl chloroform, 25% propane and dimethyl ether, and 10% inert ingredients) during which the worker reported often feeling dizzy or intoxicated. Three months following removal of the worker from exposure, liver function tests, although still abnormal, were significantly improved. Other case reports support these findings (Hodgson *et al.*, 1989; Halevy *et al.*, 1980).

Six male volunteers were exposed to 35 and 350 ppm methyl chloroform for 6-hours on two separate occasions (Nolan *et al.*, 1984). Absorption was determined to be 25% of the inhaled

dose. Of the absorbed dose, 91% was excreted unchanged in the expired air. Although the odor was perceptible for the duration of the exposure, no subjective symptoms were reported by the volunteers.

V. Effects of Animal Exposure

Gerbils (4/sex/dose plus 24 sex-matched control animals) were continuously exposed to 70, 210, or 1000 ppm methyl chloroform for 3 months (Rosengren *et al.*, 1985). A 4-month (solvent-free) recovery period following exposure was included to evaluate "lasting or permanent changes." Body weights were not changed significantly as a result of exposure. Brain weights in the animals in the 1000 ppm dose group were significantly decreased. Fibrillary astrocytes are formed in the brain in response to injury. Brain injury in methyl chloroform exposed gerbils was evaluated by detection of glial fibrillary acidic (GFA) protein, the main protein subunit of astroglial filaments. Increased levels of GFA protein were detected in the sensorimotor cerebral cortex of animals exposed to 210 or 1000 ppm methyl chloroform.

A later study in gerbils examined the effects of a 3-month continuous exposure to 70 ppm methyl chloroform followed by a 4-month recovery period (Karlsson *et al.*, 1987). DNA content was significantly decreased in three areas of the brain: posterior cerebellar hemisphere, anterior cerebellar vermis, and hippocampus. The authors contended that depressions in DNA content reflect decreased cell density.

No evidence of peripheral neuropathy or other neurotoxicity was detected in rats exposed to 200, 620, or 2000 ppm methyl chloroform 6 hours per day, 5 days per week for 13 weeks (Mattson *et al.*, 1993). The study included a functional observational test battery and measured visual, somatosensory, auditory and caudal nerve-evoked potentials. Histopathology of the brain, spinal cord, peripheral nerves and limb muscles was also examined at the end of the 13-week exposure.

Forty percent of all mice continuously exposed to 1000 ppm methyl chloroform for 14 weeks exhibited evidence of hepatocellular necrosis (McNutt *et al.*, 1975). A statistically significant increase in liver weight per body mass was observed throughout the study. Electron microscopy revealed accumulation of triglyceride droplets in the centrilobular hepatocytes following one week of exposure to 1000 ppm methyl chloroform. After 4 weeks of exposure, cytoplasmic alterations in centrilobular hepatocytes included a loss of polyribosomes and increased smooth endoplasmic reticulum. Similar changes observed occasionally in hepatocytes from mice exposed to 250 ppm were not as dramatic.

Mild hepatocellular changes were observed in rats exposed to 1500 ppm methyl chloroform 6 hours per day, 5 days per week for 6, 12, and 18 months (Quast *et al.*, 1988). At 24 months, these slight effects were no longer discernible due to confounding geriatric changes. No hepatocellular changes or other adverse effects were observed in rats exposed to 150 or 500 ppm methyl chloroform for up to 24 months.

The developmental toxicity of inhaled methyl chloroform was studied in CD-1 mice. Mice were exposed on gestation days 12 through 17 to either 2000 ppm methyl chloroform for 17 hours per

day or 8000 ppm methyl chloroform for 1 hour three times per day (Jones *et al*., 1996). There were no effects on pregnancy outcome, but exposed pups has reduced weight gain, had poorer results on motor coordination tests and showed delays in negative geotaxis (orienting towards the top of a sloped screen).

VI. Derivation of Chronic Reference Exposure Level (REL)

Study	Rosengren *et al.* (1985)
Study population	Mongolian gerbils (4/sex/dose)
Exposure method	Whole-body inhalation exposure
Critical effects	Astrogliosis in the sensorimotor cerebral cortex
LOAEL	210 ppm
NOAEL	70 ppm
Exposure continuity	Continuous
Average experimental exposure	70 ppm for NOAEL group
Human equivalent concentration	Not derived (species-specific data for gerbils unavailable to validate assumption of RGDR=1)
Exposure duration	3 months
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	300
Inhalation reference exposure level	0.2 ppm (200 ppb; 1 mg/m^3; 1,000 µg/m^3)

VII. Data Strengths and Limitations for Development of the REL

Case reports indicate that the nervous system and the liver are targets of the toxicity of methyl chloroform (House *et al.*, 1994; Liss, 1988; Howse *et al.*, 1989; Cohen and Frank, 1994). The largest of the epidemiological studies (Kramer *et al.*, 1978; Maroni *et al.*, 1977), however, did not identify adverse effects as a result of chronic methyl chloroform exposure. The Kramer *et al.* (1978) study limited its evaluation to changes in blood pressure, heart rate, or electrocardiogram and exposure levels were only characterized as less than 250 ppm. Maroni *et al.* (1977) conducted their study among 22 women exposed occupationally to methyl chloroform levels as low as 110 ppm. Although the subjects were evaluated specifically for signs of neurotoxicity, the small sample size limits conclusions that can be drawn from their failure to identify adverse effects in this population. If no effects are associated with the exposures in the 2 studies (Kramer *et al.*, 1978; Maroni *et al.*, 1977), the REL predicted would be approximately 3 ppm.

Data from animal studies generally support the findings of the case reports from human exposures. Both neurotoxicity and hepatotoxicity have been identified among animals exposed by inhalation to methyl chloroform. The adverse effect observed at the lowest level in these studies was the development of astrogliosis in the brains of gerbils exposed for 3 months to 210 ppm methyl chloroform (Rosengren *et al.*, 1985). A no-observed-adverse-effect-level (NOAEL) in this study was 70 ppm methyl chloroform. A subsequent study identified a more subtle change in the brains of gerbils exposed similarly to 70 ppm methyl chloroform, with slightly

decreased DNA content found in several discrete brain regions of exposed animals. However, the relationship between tissue DNA content and cell density as an indication of adverse effect in the brain was considered too tenuous for the development of a guidance value for chronic exposure to methyl chloroform.

The major strengths of the REL for methyl chloroform are the observation of the NOAEL and the continuous subchronic exposure regimen. The major uncertainties are the lack of human exposure data, the lack of dose-response information, and the lack of comprehensive multi-organ effects data.

VIII. References

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